UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Date: March 12, 2010

SUBJECT: Review of Enhanced Reporting of 2008 Pet Spot-on Incidents

PC Code: See page 2 of this document
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0055303
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.: N/A
40 CFR: N/A

Ver.Apr.08

FROM: Kit Farwell, D.V.M., D.A.B.T.
Risk Assessment Branch VII
Health Effects Division (7509P)
Office of Pesticide Programs

THROUGH: Mary Manibusan, Ph.D., Branch Chief
Toxicology and Epidemiology Branch
Health Effects Division (7509P)
Office of Pesticide Programs

TO: Kimberly Nesci, Product Review Manager
Insecticide Branch
Registration Division (7505P)
Office of Pesticide Programs

Following are conclusions and data evaluation records of 2008 pet spot-on incident reports.

The EPA technical reviewers were Byron Backus, Princess Campbell, and Kimberly Nesci of the Registration Division, Melba Morrow, and Sanyvette Williams of the Antimicrobial Division, Jean Holmes of the Environmental Fate and Effects Division, and Marion Copley, Larry Brooks, Mary Manibusan, and Kit Farwell of the Health Effects Division.

Incident reports for the following spot-on products for dogs were reviewed.

Registration #	Active Ingredient (PC Code)
2517-80	cyphenothrin (129013), pyriproxyfen (129032)
2517-85	cyphenothrin (129013)
2596-151	phenothrin (069005)
2596-150	phenothrin (069005), S-methoprene (105402)
2517-94	permethrin (109701), pyriproxyfen (129032)
2724-497	permethrin (109701), S-methoprene (105402)
2724-497-270	permethrin (109701), S-methoprene (105402)
83399-6	permethrin (109701) , dinotefuran (044312), pyriproxyfen (129032)
11556-132, -133, -134, -135	permethrin (109701), imidacloprid (129099)
11556-117, -119, -120, -122	imidacloprid (129099)
80490-2	amitraz (106201), metaflumizone (281250)
65331-3	fipronil (129121)
65331-5	fipronil (129121), S-methoprene (105402)

Incident reports for the following pet spot-on products for cats were reviewed.

Registration #	Active Ingredient (PC Code)
80490-3	metaflumizone (281250)
11556-116, -118	imidacloprid (129099)
83399-9	dinotefuran (044312), pyriproxyfen (129032)
65331-2	fipronil (129121)
65331-4	fipronil (129121), S-methoprene (105402)
69332-3-2517	etofenprox (128965), pyriproxyfen (129032),
2724-504	etofenprox (128965), S-methoprene (105402)
2724-504-270	etofenprox (128965), S-methoprene (105402)
2724-504-2596	etofenprox (128965), S-methoprene (105402)
2596-147	S-methoprene (105402)
2724-488	S-methoprene (105402)

Review of 2008 Incident Reports for Dog and Cat Spot-on Pesticides

Executive Summary:

The spot-on pesticides are used for monthly control of fleas, ticks, or other external parasites. They are applied from a small tube to the back of the pet. Control of these external parasites is desirable because they can cause discomfort to the pet, skin disease, and anemia. In addition, fleas can transmit tapeworms to pets, and ticks can cause tick paralysis and can transmit diseases such as Lyme disease and Rocky Mountain Spotted Fever, to both pets and people. Severe flea infestations can result in flea bites to people. There is thus a need for safe and effective control of these external parasites.

In 2009, EPA became increasingly concerned about the large number of incident reports involving pet flea and tick spot-on products. Because details about the incidents were not available, EPA required enhanced reporting of incidents for the year 2008 by the registrants. An internal and external review of those data has been conducted by EPA and this document summarizes the results of the reviews.

A comparison of the absolute numbers of incidents among the different spot-on products in this report is not appropriate. This is because some products may have more incidents than other products because more of that product is sold and because incident information is voluntarily submitted by pet owners, with varying levels of detailed information, and routine reporting is sometimes lacking. The incidents have not been verified and may have causes other than exposure to the pesticide.

Based on EPA's systematic review of the enhanced incident reports, the following conclusions are provided.

General Findings for Dogs:

- The main organ systems affected were the dermal, gastrointestinal, and nervous systems. Clinical signs included such effects as vomiting, diarrhea, salivation, itching, hair loss, skin ulceration, lethargy, nervousness, ataxia, tremors, and seizure. Although most incidents were classified minor, all products had some deaths and/or incidents classified as major (See the Appendix for a definition of major, moderate, and minor incidents).
- Mixed breed dogs were most commonly reported because of their popularity. Although the number and popularity of dogs of each breed is not known, the number of American Kennel Club registrations per year was used as a measure of breed popularity, and it was found that small breed dogs were more commonly affected with the number of incidents out of proportion to their popularity for some products.
- Most incidents in dogs occurred in pets less than 3 years old, which may be due to the age at first exposure to the pesticide. Use of product in underage animals was relatively rare, accounting for less than 7% of incidents for most products.
- The majority of incidents in dogs occurred in dogs weighing approximately 10-20 pounds, probably because of the popularity of small breed dogs. However, as

noted above, there were more incidents in small breed dogs for some products than would be indicated by their AKC rankings.
- Some incidents occurred when product labeled for a larger dog was applied to a smaller dog, with this type of misuse varying between the dog products.

General Findings for Cats:

- The main organ systems affected were the dermal, gastrointestinal, and nervous systems. Clinical signs in cats were similar to those in dogs noted above.
- Most incidents occurred in domestic short hair cats because that is the most common type of cat.
- Most incidents occurred in cats weighing between 5 and 15 pounds because most cats fall in that weight range. A number of incidents occurred in cats dosed with product meant for a heavier cat, although it's possible that many cat owners estimate their cat's weight and do not know the actual weight, either for selection of the appropriate product, or when reporting the incident.
- An important problem was the inappropriate treatment of cats with dog product, with some dog products having a higher percentage of incidents in cats than other dog products.

Additional Findings:

- "Inert" ingredients in the products serve as a solvent and aid in dispersal of the pesticide. These ingredients may have been responsible for a number of the incidents as some have toxic properties, although additional analyses are necessary before an association can be established. A complete review on inerts is pending.
- The spot-on labels provide instructions for safe uses with warnings to prevent misuse and the consequences of misuse, *e.g.* against using dog products on cats or not to use on aged or sick animals, but were found to not always be effective in preventing misuse. Sometimes the warnings did not stand out from the rest of the required label information. Many labels have pictograms showing the method of proper application, but some do not. Many products have the same brand name for the cat and dog product and other products have the same brand name associated with different active ingredients.
- The companion animal safety studies did not accurately predict toxicity seen in the incident reports. For example, safety studies rely upon Beagle dogs, but Beagles were not a sensitive breed for predicting adverse incidents in dogs as shown in this incident analysis. The guideline for this study was harmonized with study requirements by the FDA Center for Veterinary Medicine. The FDA also requires clinical trials before registration, but a similar study is not required by EPA.

Next Steps:

- Risk managers in EPA worked closely with reviewers of this technical document of the spot-ons; the risk mitigation options that they evaluate will be presented separately from this report.
- This report is based on 2008 incident data. Continued monitoring of the incident data is necessary to determine what changes have been effective; therefore this review should be an ongoing process, looking for trends over time, with the awareness that the number of incidents reported in the short term may spike because of increased publicity.
- More consistent data reporting parameters for incident reporting are needed and the EPA Office of Pesticide Programs is working towards a more systematic electronic incident data system. In addition, a closer evaluation of our requirements to determine what specific changes are needed to provide a stronger basis for safety determinations for these spot-on products, as well as other pet products, will be made.

I. Background:

EPA is responsible for assuring that pesticides sold in the United States do not cause unreasonable risks when they are used according to label directions and precautions. If evidence arises to challenge the safety of a registered pesticide product, EPA reviews scientific data and takes action if necessary to reduce or eliminate the risks. Some flea and tick products are drugs that are regulated by the Food and Drug Administration. The EPA-registered pesticides can be identified by an EPA registration number on the packaging.

One group of pesticides regulated by EPA is the dog and cat spot-on pesticides. The spot-on pesticides are used for monthly control of fleas, ticks, or other external parasites. The spot-ons are applied from a small tube to the back of the pet. Control of these external parasites is desirable because they can cause discomfort to the pet, skin disease, and anemia. In addition, fleas can transmit tapeworms to pets, and ticks can cause tick paralysis and can transmit diseases such as Lyme disease and Rocky Mountain Spotted Fever, to both pets and people. Severe flea infestations can result in flea bites to people. There is thus a need for safe and effective control of these external parasites. Spot-on pesticides are popular with pet owners because they are a convenient and effective means of flea control on pets that have to a great extent supplanted the use of pet shampoos and dips.

In 2009, the U.S. Environmental Protection Agency and Health Canada Pest Management Regulatory Agency (PMRA) became increasingly concerned about the large number of incident reports involving pet flea and tick treatments with spot-on products. Because of this concern, EPA and PMRA communicated with the public and issued advisories to the public on April 16, 2009. The advisory issued by EPA described the incidents as ranging "from mild effects such as skin irritation to more serious effects such as seizures and, in some cases, the death of pets"[1]. Subsequently, on May 5, 2009, EPA met with the registrants of U.S.-registered spot-on products and informed spot-on pet product registrants of the need to perform a more detailed analysis of the incident data[2].

There was a need for more detailed data about the incidents because most registrants, as required by law, currently provide only aggregate summary reports about incidents. The aggregate reports only provide the number and severity of incidents, but details about each incident are not reported. Therefore, a request for enhanced reporting of spot-on incident data for the year 2008 was made at the May 5, 2009 EPA meeting with registrants and interested stakeholders. Further details on the enhanced reporting were provided to the registrants in a May 26 email. The requested data list was comprehensive and the requested due date for submission by the registrants was July, 2009.

EPA requested that the following data be submitted in spreadsheet format: EPA registration #, product name, lot #, formulation (basic, alternate), where purchased by pet

[1] http://www.epa.gov/pesticides/health/flea-tick-control.html
[2] http://www.epa.gov/pesticides/health/spot-on-meeting-may2009.pdf

owner, active ingredient(s) , weight range for product, date of incident, state in which incident occurred, case #, species, breed, age, sex, body weight, route of exposure, application site, body system affected, clinical signs, time to onset, duration of signs, whether treated by veterinarian, treatment provided, whether this was first time product used, whether incident was due to misuse, if pet was treated with other pesticide or drug, any known precondition, EPA severity code, certainty index, outcome, text narrative of incident, and sales data.

A team of expert veterinarians/toxicologists from several divisions in the EPA Office of Pesticide Programs was assembled to expeditiously evaluate the forthcoming enhanced incident data. The first meeting was held on May 12 2009 and weekly meetings were held which included the Health Canada Pest Management Regulatory Authority and the FDA Center for Veterinary Medicine by teleconference.

This document describes the analysis of incidents occurring in the U.S with EPA-registered pesticides. The PMRA is releasing a separate report of spot-on incidents in Canada with PMRA-registered spot-on products.

II. Methods

Data from the registrants were received from mid-July through August, and in some cases in September. The first step was "cleanup" of the data submitted by the registrants. This was the most difficult and time consuming part of the evaluation.

It is acknowledged that the registrants were given a very short timeframe for data submission and the process was reportedly difficult and time consuming in many cases. Conversion of their databases to spreadsheet format, as requested by EPA, was apparently not easy and sometimes inappropriate data was included in the spreadsheet cells (*e.g.*, clinical signs mixed in with route information). Two registrants sent caveats about the problems encountered in compiling the data requested by EPA.

Submissions varied in quality among the registrants, and the inconsistent terms, spellings, and formatting, both between and within submissions from the registrants, made sorting of the data difficult. However, all registrants responded quickly when there were questions or requests for clarification about the data.

Not all of the data requested by EPA was available for all of the products because some information was not commonly collected by the registrants or simply because the pet owner did not have the information available. In many cases, some of the data were provided by the registrant in a text narrative but were not available in a separate cell in the spreadsheet.

Incidents which were not evaluated: Not all incident reports were included in the evaluations by EPA. Incidents which were generally not included:

- Incidents with no EPA registration number
- Incidents from other countries
- Efficacy reports
- Incidents which were considered generally ambiguous
- Incidents which also involved use of other pesticides or drugs because effects may have been associated with the other product
- Incidents which involved multiple animals because it was difficult to tell which animal was affected and to what degree
- Multiple reports or contacts with the registrant for the same incident

Data tables: Once "cleaned up", the registrant spreadsheets were entered into Microsoft Access for sorting and tables for the above parameters were provided to the EPA technical reviewers.

Template for incident review: The Team developed a template for review of the data which included parameters commonly collected by the registrants and which could identify potential problems and susceptible pet populations for potential mitigation, if appropriate.

The parameters which the Team selected to be evaluated included:

- Number and severity of incidents by different routes of exposure
- Number and severity of incidents in different age groups
- Number and severity of incidents in different weight groups
- Number of incidents for each breed
- Number of clinical signs and/or organ system affected
- Number of incidents due to misuse or inappropriate exposure
    - in the wrong species, *e.g.* dog product used on a cat
    - in a pet weighing less than the labeled weight range
    - in a pet younger than indicated on the label.
- Results of companion animal safety testing
- Results of toxicity testing in lab animals

A. Data Analysis

1. Internal Peer Review

Information was exchanged with a number of groups to develop standardized reporting and terminology consistent with other organizations. These included presentations by Dr. John Baker of FDA Center for Veterinary Medicine, Dr. Alan Rawling of PV-Works incident database software, and Dr. Rick Kingston of SafetyCall Adverse Event Call Center. EPA and Health Canada's PMRA attended a meeting of the "Monitored Adverse Reaction Committee" at FDA Center for Veterinary Medicine (CVM) to learn how FDA/CVM evaluates adverse events.

The following people and offices were consulted: Dr. David Stone of the National Pesticide Information Center; Dr. Kia Bensen of Prosar Product Safety Call Center; Dr. Safdar Khan of the Animal Poison Control Center of the American Society for the Prevention of Cruelty to Animals (ASPCA); the American Veterinary Medical Association (AVMA) Practitioner's Advisory Committee; the AVMA Council on Biologic and Therapeutic Agents; Dr. Elizabeth Curry-Galvin, Director of Scientific Activities of the AVMA; and Dr. Geoffrey Calvert of the National Institute for Occupational Safety and Health.

A template for review was developed by the Team so that each product could be reviewed and reported in a similar format. The first group of products was discussed in the weekly teleconferences with PMRA and FDA and these initial discussions resulted in changes to the reporting format. The report on each product received a formal secondary review by another Team member.

2. External Peer Review

The incident reviews underwent a comprehensive external team review. This was done in an intensive 3-day meeting from November 3-5. The Health Canada Pest Management Regulatory Authority was represented by Ms. Dana Bruce and FDA Center for Veterinary Medicine participants were Drs. John Baker and Susan Bright. A number of members of Health Canada Pest Management Regulatory Authority participated by teleconference. Dr Stephen Page, Director, Advanced Veterinary Therapeutics, Australia, joined the meeting via teleconference to provide a review of pet incident findings for Australia, the UK, and France, but did not participate in the team review of the review documents. Each review document was discussed at length for revision by the primary reviewer later.

The following parameters were evaluated for each product:

How many total A (deaths), B (major), C (moderate), D (minor) events by combined routes?
How likely was the association of spot-on treatment with the deaths?
Are cats more sensitive to dog products in terms of total number of incidents and severity?
Are small breeds more sensitive for each product?
What major organs are affected?
What was the percent misuse by age, weight, and species?
Was a wide product weight range associated with incidents?
Results from the companion animal safety study and toxicology database were evaluated.

The document reviews were revised by the EPA primary reviewer after the external peer reviews and underwent a secondary review by the EPA secondary reviewer.

B. Results

1. Interpreting the Data

The intent of this evaluation was not just to report the total number of incidents, but to describe the nature of the incidents and to identify any susceptible subpopulations or use patterns which may increase the risk of toxicity so that mitigation could be implemented

if appropriate. The individual incidents were not verified and may have had causes other than exposure to the pesticide or may have been associated with an underlying medical condition.

A comparison of the absolute numbers of incidents among the different spot-on products in this report is not appropriate. This is because the total number of incidents reported here could have been influenced by many factors, among them:

- Some products may have more incidents because they have a large market share.
- Products may have a different market niche with resulting differences in amount of misuse or tendency to report incidents by the pet owner because of the type of consumers who buy the product.
- The number of incidents may have been influenced by the ease or difficulty in reporting incidents to the different registrants.
- Data were recorded and stored differently by the different registrants.
- The number of incidents may have been influenced by negative publicity for a particular product.
- Not all incidents were evaluated in this report, although exclusion of these incidents is not believed to affect general conclusions reached in this evaluation. Not evaluated were incidents with no EPA registration number, incidents from other countries, efficacy reports, incidents which also involved use of other pesticides or drugs, or incidents with multiple animals as described in Section II of this document.

2. Results for Dogs

As described in more detail below, small breed dogs were commonly involved in incidents, with the Chihuahua, Shih Tzu, Miniature Poodle, Pomeranian, Dachshund, and Bichon Frise often over represented out of proportion to their popularity. Most incidents were in dogs weighing approximately 10-20 pounds. The percentage of incidents associated with misuse of a product meant for a heavier dog on a small dog varied between products. Most incidents occurred in dogs less than 3 years which is probably because that was the age at first exposure to the product.

Dog Breeds

Mixed breed dogs were most commonly reported, presumably because of their popularity. Small breed dogs were commonly reported for most products. This was especially true for products containing cyphenothrin and permethrin, with the number of incidents out of proportion to their popularity, as summarized below. Although the number of dogs of each breed is not known, the American Kennel Club (AKC) ranks the different breeds according to the number of registrations per year, and this ranking was used as a measure of breed popularity.

Cyphenothrin: Small breeds were very highly represented for the cyphenothrin products. The 5 breeds with the most incidents were all small dogs: Chihuahuas, Shih Tzus, Miniature Poodles, Pomeranians, and Dachshunds. These 5 small breeds accounted for

approximately 33% of the incidents with the cyphenothrin products. The high number of incidents with these products is apparently not due solely to their popularity. This is because the top 5 dogs in the AKC rankings, the Labrador Retriever, Yorkshire Terrier, German Shepherd, Golden Retriever, and Beagle accounted for only 8% of the incidents with these two products.

The high number of incidents in small breeds was confirmed with other data. EPA commissioned an analysis by the Animal Poison Control Center of the ASPCA which reported that 65% of the incidents with this product were in small breeds. The National Pesticide Information Center also reported that most incidents with cyphenothrin products were in small breeds.

Permethrin: Small breeds were also highly represented for permethrin-containing products. These products are all sold by different registrants, but the five breeds with the most incidents were very similar for all the permethrin products. Shih Tzu, Bichon Frise, Chihuahua, Yorkshire Terrier, and Maltese accounted for over a quarter of the incidents for permethrin products, and the number of incidents appeared out of proportion to their AKC rankings.

Other products: The remaining products generally tracked the AKC rankings for the most part, although Chihuahuas, Pomeranian, Shih Tzus, and the Bichon Frise, were often overrepresented in comparison to their AKC ranking.

Age

The majority of incidents in all products occurred in dogs less than three years old. Since this was such a common finding, it may reflect a common use pattern such as the age at first exposure to the product. Misuse of product in animals less than the age specified on the label was relatively rare, accounting for less than 7% of incidents for most products.

Dog Body Weight

The great majority of incidents for all products were in dogs weighing approximately 10-20 pounds. A likely explanation is the popularity of small breed dogs. However, for cyphenothrin and permethrin products, as noted above, there were many more incidents in small breed dogs than would be indicated by their AKC rankings.

Some products had a number of narrow dose ranges to cover the range of small dogs to heavy dogs, while other products had fewer and wider dose ranges. This would result in larger doses per pound for dogs at the bottom of each dose range, particularly so for dogs receiving product labeled for the smallest dogs.

For example, for one permethrin product (Reg # 2517-94), the bottom dose range is for dogs weighing less than 33 pounds, with the next weight range being 33-66 pounds. Since the dose bands overlap, a dog weighing 33 pounds could receive either the product for smaller dogs (<33 pounds) or the product for larger dogs (33-66 pounds). If the

product for smaller dogs was used, a 33 pound dog would receive only 1/6 the dose of a dog that weighed 5 pounds. On the other hand, the same 33 pound dog would receive a dose twice that of a dog weighing 66 pounds if the next higher dose were selected.

Another contributing factor may be that smaller dogs have thinner skin and a greater surface area in proportion to their body weight than larger dogs, resulting in greater absorption of product in smaller dogs than for larger dogs.

Another explanation for the number of incidents in small dogs is intentional or accidental misuse when a product labeled for a larger dog is used on a smaller dog. Pet owners may have sometimes intentionally overdosed their dogs because they found it more economical to buy product labeled for a larger dog and divide the dose for use between smaller dogs. Other pet owners may have overestimated how much their pet weighed and accidentally used product intended for a larger dog on a smaller pet. This kind of misuse varied between the dog products, ranging from approximately 4% to 78%.

For one product with a large number of incidents in small breeds (Reg 2517-80), an analysis was done of incidents in the lowest weight range to see if the dogs were dosed with product for the appropriate weight range or if incidents were due to misuse by using product meant for a larger dog. For this product, it was found that there was a substantial amount of misuse (28% of incidents for dogs in the lowest weight range), but that the majority of those dogs were dosed appropriately. Although the weight range for that product was fairly narrow (9-20 pounds), most of these incidents in small dogs were in dogs in the lower half of that product's weight range.

A similar analysis was done for the product that had the most misuse related to weight to see if the weight misuse was mostly occurring in small dogs or in dogs of all weights. It was found that weight misuse occurred in all weight groups for that product and indicates that the incidents with this product were not due to small dogs being dosed with product meant for a larger dog.

Clinical signs/Organ system

Ideally, both clinical signs and organ system should be reported, and the clinical signs could be used to characterize the effects seen in the organ system. However, for some products, only clinical signs or organ system were reported, and for others, neither were reported. Related clinical signs were sometimes combined by the EPA reviewer when appropriate.

Interpretation is difficult when only clinical signs are reported, especially when there are multiple clinical signs for an affected organ system. For example, if each dog had itching, redness, hair loss, and tremors reported, then it would appear that there were 3 times as many skin effects as neurological signs, when there were actually the same numbers of dogs with each organ system affected.

The main organ systems affected in dogs were the dermal, gastrointestinal, and nervous system. Gastrointestinal effects include signs such as vomiting, diarrhea, and salivation. Dermal effects include redness, itching, hair loss, hair color changes, sores, and skin ulceration. Nervous system effects include lethargy, nervousness, ataxia, tremors, and seizure. Some skin and nervous system effects may overlap, for example, when a dog exposed to pyrethroids has paresthesia effects which could be shown as scratching, vocalizing, or agitation. There were a number of reports of "systemic disorders" which were not helpful in describing the effects.

Severity in Dogs

The incident reports submitted by the registrant were coded for severity and are reported in the attached individual incident report reviews. There were deaths and major incidents for every dog product; most of the incidents were classified minor (See Appendix for definition of severity codes). Caution should be used in comparing the number of incident reports between products because some products may have a high number of incidents because a large number of units were sold.

3. Results for Cats

Cat Exposure to Cat Product

Analysis of incident data for cats was not as informative as for dogs in determining causative factors. Most incidents occurred in domestic short hair cats because those are the most common type of cat. Most incidents occurred in cats weighing between 5 and 15 pounds because most cats fall in that weight range. A number of incidents occurred in cats dosed with product meant for a heavier cat, although it's possible that many cat owners estimate their cat's weight and do not know the actual weight, either for selection of the appropriate product, or when reporting the incident.

Incidents were reported for all products, including 2 products containing S-methoprene as the sole active ingredient. Companion animal safety studies were not required for these products because S-methoprene, which is an insect growth regulator, is of low toxicity to mammals. There are concerns for the potential toxicity of a formulant ingredient being responsible for toxicity of these products in cats. There are no toxicity data in cats for this formulant, and cats are sensitive to many chemicals because of a decreased ability to detoxify chemicals compared to other species.

In cats, as with dogs, the major organ systems affected were dermal, gastrointestinal, and nervous systems. Common effects included dermatitis, itching, hair loss, hair color changes, salivation, lethargy, vocalization, behavioral changes, tremors, and seizures.

Cat Exposure to Dog Product

A number of incidents in cats were attributed to dog products, either because the cat was intentionally or unintentionally treated with a dog product, or through exposure to a treated dog. Many of the dog product labels have a picture of a cat struck out, a text warning of the health consequences to the cat, and/or written advice to separate treated pets. Sometimes the cat warnings did not stand out from the other information on the label and some cat products had the same name as the dog product.

Although the label warnings on dog products advising pet owners not to use the product on cats have clearly not been successful in preventing such all such use, the warnings have been effective in reducing the number of such incidents, because dog products without the label warning have a much high percentage of incidents in cats than those without the warning.

Three dog products with 45% permethrin had a high percentage of incidents in cats. Approximately 20-80% of the total incidents for these dog products were in cats. Cats had more deaths and major incidents than did dogs for each of these products.

In contrast, another product with 36% permethrin had a very small percentage of cat incidents compared to dog incidents; only approximately 2% of the total incidents for this product were in cats. This product also had a low percentage of deaths and major incidents in cats. The reason for the low relative occurrence of cat incidents for this permethrin product may be that this product is sold by veterinarians with a resulting high compliance rate for proper use and/or the fact that this product has a lower percentage of the active ingredient.

4. Formulant Ingredients

Formulant ingredients, commonly called "inerts," provide a solvent for the insecticidal active ingredient and aid in dispersal of the product. These ingredients were discussed during the review process and it was felt that they contribute to toxicity reported in some incidents. Because these ingredients are considered confidential business information, they are not reported here but should undergo continued evaluations.

5. Labels

Product labels were evaluated during the internal and external reviews as to their adequacy to prevent misuse. The labels provide instructions for safe uses with warnings to prevent misuse, *e.g.* against using dog products on cats or not to use on aged or sick animals, and often the consequences of misuse. Many labels have pictograms showing the method of proper application, but some did not. Many products have the same brand name for the cat and dog product. Sometimes the warnings did not stand out from the rest of the required label information.

6. Companion Animal Studies

The EPA companion animal safety study, Guideline 870.7200[3] was developed in 1996 to harmonize with requirements for pre-market testing by FDA Center for Veterinary Medicine. Issues about the companion animal study were presented at a Science Advisory Panel meeting in October 1996[4] before the guideline was implemented. FDA also requires clinical trials in a diverse population of pets, but clinical trials are not presently required by EPA.

The EPA guideline calls for testing at 1X, 3X, and 5X doses of the end use product in 6 animals per sex of each dose group, with the age of the animals dependent upon label claims. For evaluation of safety, the guideline states: "The targeted adequate margin of safety is 5X. Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life-

[3] http://www.epa.gov/opptsfrs/publications/Test_Guidelines/series870.htm
[4] http://www.epa.gov/scipoly/sap/meetings/1996/october/report.pdf

threatening signs)." Recently, studies in lactating or pregnant animals have been reviewed by EPA which were tested at only a 3X dose, similar to requirements by FDA.

The EPA guideline states that the companion animal study is intended to demonstrate an adequate margin of safety if the product is misused or overused, serve as a basis for product labeling, and to assure consistency and fairness in data requirements. Although not explicitly stated in the guideline, the 5X margin of safety is also intended to be protective of effects seen in a larger population because the testing is only done in a small group of animals which may not always detect toxicity occurring in a larger, more heterogonous group of animals.

Companion animal studies for the individual spot-on products were re-evaluated during the internal and external reviews and it was concluded that this study in its present form has not served to predict toxicity seen in incident reports. For example, Beagles are generally used in safety testing, but were not among the more sensitive species for incidents. Revisions and additions to the EPA guideline are being developed and should continue.

III. Overall Conclusions

- Most incidents were classified minor, but all products had deaths and major incidents.
- Major organ systems affected were dermal, gastrointestinal, and nervous system.
- Small breed dogs were affected most often for cyphenothrin and permethrin products, but also for other products.
- Chihuahuas, Pomeranians, Shih Tzus, Dachshunds and Bichon Frise were commonly affected.
- The dose range may be too wide for some products.
- Misuse or inadvertent exposure of dog product on cats is an important problem.
- Clearly label warnings against use of dog product on cats are not adequate.
- The companion animal safety study did not predict toxicity seen in the incident reports.

IV. Recommendations for Continuing Analysis

This review provided a "snapshot" of the 2008 pet spot-on incidents. Assessment of spot-on incidents should be a continuing process looking for trends over time, with the awareness that the number of incidents in the short term may increase because of increased publicity and resultant increase in reporting. There are a number of "lessons learned" during this first review that could improve the review process.

The EPA Office of Pesticide Programs would benefit from a standardized type of submission by registrants using standard terminology. Systematic submissions of incident data in the form presented in these evaluations will allow a more efficient and accurate analysis of incidents and provide a stronger basis for risk assessments. The raw data should still be submitted to allow quality assurance/quality control.

The next EPA analysis of 2009 data should better characterize the dermal toxicity and neurotoxicity reported by pet owners and should more completely assess potential causation by the formulation ingredients.

There should be more complete separation of incidents involving misuse from appropriate use. Incidents with multiple animals should be included. For weight analysis, there should be more separation of pet weight ranges and assessment as to the percentage of incidents in the upper and lower half of each weight range.

EPA is aware that the spot-on products are not static and that registrants have made recent changes and are planning changes to the products in order to reduce the number and severity of pet incidents. Future reviews by EPA should be flexible to adapt to changes in the products and to continue to monitor incidents with these products as well as new pet spot-on products currently in review.

The EPA risk managers of the spot-ons will present risk mitigation options separately from this report.

APPENDIX 1: Severity Categories

See Pesticide Registration Notice 98-4, April 3, 1998.

D-A - Domestic Animal Death
§159.184 (5)(ii)(A): "If the domestic animal died or was euthanized."
It was reported that the animal died or was euthanized as a result of exposure or as a direct complication of exposure to the pesticide.

D-B - Domestic Animal Major
§159.184 (5)(ii)(B): "If the domestic animal exhibited or was alleged to have exhibited symptoms which may have been life-threatening or resulted in residual disability."

Life-threatening effects include, but are not limited to, massive or internal hemorrhage, loss of consciousness, grand mal seizures, paralysis, cardio-respiratory depression and bronchoconstriction requiring immediate treatment. In general, life-threatening effects are any condition which, if untreated, would likely lead to death. Residual disability includes adverse effects which last for an extended period of time after the initial poisoning and may affect the life span for the animal. An example of an adverse effect which may last for an extended period of time is the case of a cat that developed severe weakness lasting for weeks to months after organophosphate exposure. An example of a residual disability that may affect the life span of an animal is the case of a dog which recovered from cholecalciferol rodenticide ingestion but is left with decreased renal function.

D-C - Domestic Animal Moderate
§159.184 (5)(ii)(C): "If the domestic animal exhibited or was alleged to have exhibited symptoms which are more pronounced, more prolonged or a more systemic nature than minor symptoms. Usually some form of treatment would have been indicated to treat the animal. Symptoms were not life-threatening and the animal has returned to its pre-exposure state of health with no additional residual disability."

Effects include, but are not limited to, corneal abrasion, difficulty breathing, hyperthermia, isolated focal seizures, gastrointestinal symptoms leading to dehydration, caustic injury to mouth or esophagus, severe muscle weakness, incoordination, tremors and hives. More prolonged effects are those that last one month or longer, such as a persistent skin rash.

D-D - Domestic Animal Minor
§159.184 (5)(ii)(D): "If the domestic animal was alleged to have exhibited symptoms, but they were minimally bothersome. The symptoms resolved rapidly and usually involved skin, eye or respiratory irritation."

Effects include, but are not limited to, excessive salivation, skin rash, itching, conjunctivitis, lethargy, transient cough, mild gastrointestinal symptoms of a short duration and minor behavioral changes such as agitation and hyperactivity.

D-E - Symptoms Unknown or Unspecified

§159.184 (5)(ii)(E): "If symptoms are unknown or not specified."

A domestic animal has been exposed to a pesticide and the registrant is aware or has been informed that the domestic animal has suffered a toxic or adverse effect whose symptoms are unknown or not specified.

APPENDIX 2: Peer Review Meeting Notes

USEPA/PMRA/USFDA Spot-On Pet Product Technical Peer Review
November 3-5, 2009
Meeting Minutes

On November 3-5, 2009, the US EPA, US FDA, and Canada's PMRA held a technical peer review meeting to discuss the data review of the spot-on pet product incident information.

Objective: To perform a systematic scientific comprehensive review of all enhanced pet incident data for spot-on pet products and animal toxicology data, and to determine any universally applicable findings associated with these products as a whole.

This was a global meeting with participation from Canada and Australia.

Attendees: US EPA: Marion Copley, Kimberly Nesci, Mary Manibusan, Kit Farwell, Princess Campbell, Byron Backus, Khin Oo, Jean Holmes, Larry Brooks, Jessica Kidwell, Jeff Herndon, Tina Levine, Lois Rossi, Debbie McCall; Canada PMRA: Dana Bruce, Vicky Godfrey, Shane Prodan, Brenda Linke, Pierre Therriault, Wendy Bruce; US FDA: John Baker, Susan Bright; Australia: Stephen Page

Tuesday, November 3, 2009

FDA/CVM in Rockville, MD (morning):

Team members from OPP and PMRA attended a meeting at FDA Center for Veterinary Medicine to learn how FDA evaluates animal adverse event data/information. The meeting of the USFDA "Monitored Adverse Reaction Committee" is held every 2 months and led by Dr. John Baker who is also participating on the OPP pet incident data review for Spot-on products. Pre-marketing (safety and effectiveness testing) and post-marketing (adverse events) teams evaluated mitigation options for adverse events in animals treated with FDA-approved products. Adverse events in many different products were evaluated.

Crystal City (afternoon):

Larry Brooks discussed how the enhanced data were handled. Data from seven companies were received in spreadsheets. The seven companies included Sergeant's, Fort Dodge, Bayer, Summit, Merial, Hartz, and Wellmark. The data were first "cleaned up" and imported into Microsoft Access for sorting, then exported to MS Excel to create tables reporting incidents by severity, exposure route, age, breed, gender, signs/symptoms, body weight, and body weight relative to the product weight range.

The data were organized in a short time-frame considering the difficulty in "cleaning up" the data. Because the data were prepared by the registrants on short notice, the data varied in quality and there were often inconsistencies in terminology, spelling, and formats both between companies and within the same spreadsheet. Two companies sent caveats concerning these problems with their submissions. Sometimes there were multiple information values in the same cell (breed + species + age, for example). The OPP Companion Animal Team (CAT) team included Kit Farwell, Byron Backus, Marion Copley, Jean Holmes, Melba Morrow, Princess Campbell, Larry Brooks, Mary Manibusan, Sanyvette Williams, and Kimberly Nesci. The data were then carefully reviewed by the CAT and detailed DERs were then prepared for each product.

Not evaluated were incidents with multiple animals, repeat records for the same incident, non-USA incidents, incidents with no registration #, species not named, and ambiguous data.

Thoughts for the future: Next time the team would like to do the following:

1) an analysis of incidents with multiple animals,
2) look at secondary exposure by grooming another animal,
3) provide better characterization of dermal toxicity and neurotoxicity;
4) do a more thorough analysis to see if we agreed on severity classification by registrants,
5) tables for age and weights should be adjusted for individual products rather than be the same for all,
6) an analysis of the dose to which pets were exposed,
7) more complete analysis of inerts,
8) look at rare but serious toxicities (we discounted the rare effects)

Wednesday, Nov 4 and Thursday, Nov 5, 2009

Lois Rossi provided the opening remarks to start the meeting.
Mary Manibusan was the facilitator of the meeting.

The following spot on pet incident product data were presented by the primary reviewers or their designate over these two days and discussed in detail:

Sergeants (Kit Farwell, Princess Campbell)
Fort Dodge (Kit Farwell)
Bayer (Byron Backus)
Summit (Melba Morrow, Kit Farwell/Sanyvette Williams)
Merial (Melba Morrow-dogs, Kit Farwell)
Hartz (Jean Holmes, Kit Farwell/Sanyvette Williams)
Wellmark (Marion Copley/Jean Holmes)

Parameters looked at for each product included:

How many total A (deaths), B (major), C (moderate), D (minor) by combined routes?
How likely are the deaths?
Are cats more sensitive to dog products in terms of total number of incidents and severity?
Are small breeds more sensitive for each product?
What major organs are affected?
What was the percent misuse by age, weight, species?
What effect did the product weight range have?

Dr John Baker gave an overview of the term Therapeutic Index. Therapeutic Index is defined as the range between the Minimum Effective Concentration (MEC) and the Maximum Safe Concentration (MSC). It is a range between risk and benefit. It is important to be able to predict the concentration-response relationship of a drug. If the Maximum Safe Concentration is close to the Minimum Effective Concentration, the therapeutic index is narrow. This has high variability and is unpredictable. If one can't predict, one needs to do therapeutic dose monitoring. Effects generally occur within 72 hours. For products with a narrow therapeutic index, it is crucial to find the lowest effective dose. A dose rationale is very important. Dr Baker pointed out that some of the incidents reported may be due to the narrow therapeutic index. It is desirable to be mid-way between MEC and MSC (minimum effective dose and maximum safe concentration). If a product has high variability in bioavailability, then there can be big problem – exposure may vary by 5X. The FDA/CVM does clinical field trials.

RD pointed out that some registrants are proactively addressing the dose issues with their products.

Theoretically, the EPA's companion animal safety studies give a 5x safety margin and should demonstrate no or minor effects at 3x the labeled dose. The companion animal studies generally use Beagles although Beagles don't seem to be very sensitive to many products.

Key findings of each product are listed in the table at the end of these meeting minutes.

Australia:

Dr Stephen Page, Director, Advanced Veterinary Therapeutics, joined the meeting via teleconference on the afternoon of the last day to provide a review of the pet incident findings for Australia, the UK, and France. He discussed how a review of published literature clearly established that intoxication of cats via primary or secondary exposure to products containing high (400 g/l or higher) concentrations of permethrin (permethrin spot on or PSO products) is a worldwide phenomenon that has been occurring for more than 10 years. An Australian survey of practitioners showed PSO intoxication was widespread throughout Australia with a reported mortality rate of around 22%. An assessment of the situation in the UK and France confirmed the global extent of PSO

intoxication in cats. It was noted that the addition of warning statements to PSO products did not reduce the number of incidents. Several factors are contributing to the increase of incidents of permethrin intoxication in cats. First, cats have an unusual sensitivity to permethrin. 100 mg/kg is a lethal dose to cats. Second, permethrin products are widely available over the counter, with cat and dog products mixed together on store shelves. Third, people don't read the label warnings. There is a low level of awareness by the general population that cats are sensitive to permethrins. Fourth, people don't understand the label warnings and pictograms. A survey of cat owners found that some didn't understand the symbol of "no cats". A demographic survey found that low literacy was not associated with increased incidents. (Dr Page will send this survey to us.) A PSO Steering Committee formed by the Australian Veterinary Association in early 2009 has commissioned market research to determine the characteristics of effective label warnings and has worked to develop label changes and an accompanying communication and awareness program for implementation in 2010.

APPENDIX 3: Summary of External Peer Review

PRODUCT	CATS SENSITIVE	BREEDS	WT pounds	AGE	MISUSE?	ORGAN SYSTEMS/ CLINICAL SIGNS	LABEL
Sergeant's 2517-80 Dog 2008 data Cyphenothrin 40% Pyriproxyfen 2% >12 weeks, 9-20, 21-39, 40-60, >61#	2% incidents in cats. Yes, more severity	Chihuahua, Shih Tzu, Miniature Poodle, Pomeranian, Dachshund, Yorkie, Maltese, Pug, Lab	9-20 (46%)	< 3 years old	44% under weight, 2% under age, 2% cats	Erythema, sores, pruritis, irritation; Vomiting, salivation; Tremors	Schematic for application – neck to mid back, Cat strike out warning front and back, text cat warning in red.
Sergeant's 2517-80 Dog 2007 data	1% incidents in cats Yes, more severe	Chihuahua, Shih Tzu, Dachshund, Miniature Poodle, Pomeranian, Pug, Yorkie, Bichon Frise, Lab	9-20 (51%)	< 3 years old	30% under weight 1% under age 1% cats	Neurological, GI Skin, Respiratory, Ocular	- - -
Sergeant's 2517-80 Dog Animal Poison Control Center 1/1/07 – 4/30/09	1% incidents in cats. Yes, more severe	65% small breeds	<22	Mostly < 3 years	21% under weight, 1% under age, 1% cats	Salivation, vomiting, pruritus, agitation, restless, tremors	- - -
Sergeant's 2517-80 Dog NPIC Report 2009 data		Small breeds	<25			Skin, excited, tremors, 1 seizure, GI	- - -
Sergeant's 2517-85 Dog Cyphenothrin 40% >12 weeks, 9-20, 21-39, 40-60, >61#	2% incidents in cats Yes, more severe	Chihuahua, Shih Tzu, Pomeranian, Miniature Poodle, Dachshund, Pug, Pit Bull Terrier, Beagle, Lab	9-20 (47%)	Mostly < 3 years	39% under weight 4% under age 2% cats	Agitated, itching, wound, erythema, vomiting, vocalization, seizure	Schematic for application – neck to mid back, Cat strike out warning front and back, text cat warning in red.
Hartz 2596-151 Dog Phenothrin 85.7% >12 weeks 4-15, 16-30, 31-60, >60#	2% incidents in cats. Only 9 cat incidents, but 7 of those were deaths.	Chihuahua, Lab Retriever, Yorkshire Terrier, German Shepherd, Pit Bull, Pomeranian, Shih Tzu	4-8# (24%)	<1 year	76% underweight 7% underage 2% in cats clarify misuse with deaths??	Neurological, gastrointestinal, dermatological, lethargy, vomiting, pruritus	Schematic along back. Cat strikeout and text warning.
Hartz 2596-150 Phenothrin 85.7% S-Methoprene 2.3% >12 weeks 4-15, 16-30, 31-60, >60#	10% incidents in cats, more severe	Chihuahua, Lab Retriever, Yorkshire Terrier, Boxer, Shih Tzu, Dachshund	5-11# (27%)	1-2	68% underweight 4% underage 10% in cats	Dermal, gastrointestinal, neurological, vomiting, lethargy, pruritus	Schematic along back. Cat strikeout and text warning.
Sergeant's 2517-94 Dog Permethrin 45% Pyriproxyfen 1.9% >12 weeks, ≤33, 33-66, ≥66#	82% incidents are in cats. more severe	Chihuahua, Miniature Dachshund, Miniature Poodle, Pomeranian, Shih Tzu	9-21 (46%)	1 – 3 years	23% under wt 5% under age 82% cats	No report on body systems	Schematic for application – between shoulder blades, Cat strike out warning front and back, text cat warning in red.

PRODUCT	CATS SENSITIVE	BREEDS	WT pounds	AGE	MISUSE?	ORGAN SYSTEMS/ CLINICAL SIGNS	LABEL
Wellmark 2724-497 Dog and 497-270 Dog combined Permethrin 45% S-Methoprene 3% > 6 months <15, 16-30, 31-60, >60#	23% incidents in cats. more severe	Shih Tzu, Bichon Frise, Chihuahua, Maltese, Yorkshire Terrier	5-11# (31%)	1-2	10-15% underweight 10% underage 23% in cats	Nervous system, dermal, behavioral, pruritus, lethargy, agitation	Between shoulder blades and base of tail. Cat strikeout and cat warnings in red.
Summit 83399-6 dog Permethrin 36.08% Dinotefuran 4.95% Pyriproxyfen 0.44% >7 weeks 2.5-20, 21-55, 56-95, >95	2% incidents in cats. more severe	Shih Tzu, Lab, Chihuahua, Yorkshire Terrier, Bichon frise	11-21 (30%)	<5 yrs	4% underweight minor age misuse 2% in cats	Skin, pruritus, dermatitis, emesis	Schematic. Small dogs: 1 spot on neck, medium dogs: 3 spots along back, large dogs: 4 spots along back. Cat strikeout and text warning.
Bayer 11556-132, 133, 134, 135 Dog Permethrin 44% Imidacloprid 8.8% >7 weeks ≤10, 11-20, 21-55, >55#	24% incidents in cats, more severe	Shih Tzu, Bichon Frise, Yorkshire Terrier, Maltese, Chihuahua,	11-21# (34%)	<3 yrs	10% underweight minor age misuse 24% incidents are in cats	Dermal, behavioral, systemic disorders, general signs, neurological signs	Schematic, between shoulder blades. Cat strikeout and text warning.
Bayer 11556-117, 119, 120, 122 Dog Imidacloprid 9.1% >7 weeks ≤10, 11-20, 21-55, >55#	43% incidents in cats, but not more severe	Labrador retriever, Chihuahua, Yorkshire Terrier, Pomeranian, Shih Tzu	11-21 # (28%)	< 3 yrs	23% underweight minor age misuse 43% incidents are in cats	Digestive, hyperactivity, lethargy, neurological signs, euthanized, lethargy, blood in vomit, systemic disorders	Schematic, between shoulder blades. No cat warning.
Fort Dodge 80490-2 Dog Amitraz 14.34% Metaflumizone 14.34% >8 weeks <11, 11-22, 22-55, 55-88, 88-110#	1% incidents are in cats. No – only 28 minor cat incidents.	No breed sensitivity, but Siberian husky and Chihuahua stood out	11-21 (16%)	1-3 years	wt misuse unknown <1% age misuse 1% in cats strictly sold by vets	Lethargy, skin lesions, ataxia, application site hair change may be due to ulceration and skin grow back.	No schematic. Label changed to base of skull in 2009. Cat strikeout and text warning.
Merial 65331-3 Dog Fipronil 9.7% <8 weeks <22, 23-44, 45-88, 89-132 #	7% incidents in cats. not more severe	Lab Retrievers, Yorkshire Terrier, Golden Retriever, Maltese, Pug, Shih Tzu, Chihuahua	11-21 (23%)	<1 yrs	7% underweight and 7% in cats	Systemic disorder, digestive tract, skin appendage, application site disorder, neurological	Apply to skin between shoulder blades. Label states do not use on rabbits. Do not use on other animals.
Merial 655331-5 Dog Fipronil 9.8% S-Methoprene 8.8% >8 weeks <22, 23-44, 45-88, 89-132 #	4% incidents in cats. not more severe	Labrador Retriever, Yorkshire Terrier, Shih Tzu, Golden Retriever, Bichon Frise, Chihuahua	11-21 (21%)	<2 yrs	5% underweight 4% in cats	Application site disorders, skin appendage, systemic, digestive, behavioral	Apply to skin between shoulder blades. Label states do not use on rabbits. Do not use on other animals.

PRODUCT	CATS SENSITIVE	BREEDS	WT pounds	AGE	MISUSE?	ORGAN SYSTEMS/ CLINICAL SIGNS	LABEL
Fort Dodge 80490-3 Cat Metaflumizone 18.53% >8 weeks <9#, >9#	- -	Domestic short hair	not available	< 3 yr	minor	Dermal application site, digestive tract, systemic disorders, dermatitis, pruritus, hair changes, lethargy	No schematic, same name as dog product
Bayer 11556-116 and -118 Cat Imidacloprid 9.1% >8 weeks <9, >9#	- -	- - -	5-11#	<3	minor age misuse 11% under wt	Salivation, drooling, self grooming leads to anorexia, digestive and dermal effects	Schematic, base of skull
Summit 83399-9 Cat Dinotefuran 22% Pyriproxyfen 3% >8 weeks. <9, >9#	--	DSH	--	No influence	13% underweight	Neurological, dermal, and gastrointestinal	Schematic at base of neck
Merial 655331-2 Cat Fipronil 9.7% >8 weeks No weight ranges.	--	DSH	5-16 pounds	Less than 1 year	--	Clinical signs, skin, digestive tract effects	Apply to skin between shoulder blades
Merial 65331-4 Cat Fipronil 9.8% S-Methoprene 11.8% >8 weeks No weight ranges.	- -	not available	5-16	<1 yr	not available	Application site, digestive tract, systemic, behavioral, skin appendage, neurological	Apply to skin between shoulder blades
Sergeant's 69332-3-2517 Cat Etofenprox 55% Pyriproxyfen 2.2% >12 weeks <5, >5#	- -	Domestic shorthair	5-21	1-2, up to 5	wt misuse not calc. 5% underage 4% in dogs	Vocalization, lethargy	Schematic apply behind cat's head
2724-504 and 504-270 and 504-2596 Cat combined Etofenprox 40% S-Methoprene 3.6% >12 weeks. <5, ≥5#	--	--	5-10	1-3	not available	Dermal, nervous system, behavioral changes, dermatitis	base of skull
Hartz 2596-147 Cat S-Methoprene 2.9% >12 weeks No weight range	--	Domestic short hair	11-21	<1 yr	not available	Neurological, gastrointestinal, dermal	schematic between shoulder blades

PRODUCT	CATS SENSITIVE	BREEDS	WT pounds	AGE	MISUSE?	ORGAN SYSTEMS/ CLINICAL SIGNS	LABEL
2724-488 Cat S-Methoprene 3.6% >12 weeks no weight range	--	Domestic short hair	<5	<6 months	19% underage	Nervous system, dermal, general disorders, lethargy, alopecia, pruritus, hypersalivation, tremors, seizures	base of skull